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(71) Applicant *(for all designated States except US)*: **JOHNSON & JOHNSON MEDICAL LIMITED** [GB/GB]; Erskine House, 68-73 Queen Street, Edinburgh EH2 4NH (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **SILCOCK, Derek, Walter** [GB/GB]; 2 Ash Grove, Skipton BD23 1QP (GB). **DELBONO, Michelle** [GB/GB]; 7 Priory Way, Barnoldswick BB18 5HJ (GB).

(74) Agents: **JAMES, Anthony Christopher, W.P.** et al.; Carpmaels & Ransford, 43-45 Bloomsbury Square, London WC1A 2RA (GB).

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(54) Title: HYDROCOLLOID MATERIALS FOR USE IN WOUND HEALING

(57) Abstract: A wound dressing material comprising a low-moisture hydrocolloid matrix having oxidized cellulose distributed therein. For example, a matrix of dried sodium carboxymethylcellulose gel having fibers of oxidized regenerated cellulose dispersed therein. Also provided are the use of such materials in the treatment of wounds, and the manufacture of such materials by drying aqueous gels containing dispersed particles of oxidized cellulose.

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HYDROCOLLOID MATERIALS FOR USE IN WOUND HEALING

The present invention relates to low-moisture gel compositions for use in wound dressings. The invention also relates to the manufacture of such low-moisture gel compositions, and to methods of wound treatment using such compositions.

EP-A-0918548 describes the use of oxidized celluloses, such as oxidized regenerated cellulose (ORC), for the treatment of wounds, in particular chronic wounds. Compositions are described that comprise milled ORC fibers dispersed in a 3% sodium carboxymethyl cellulose (NaCMC) aqueous hydrogel. Another example describes a composite film comprising ORC fibers dispersed in a plasticized collagen matrix. In other embodiments, the ORC fibers are dispersed in an aqueous collagen slurry and the mixture is freeze-dried to produce a collagen/ORC sponge having especially good properties for the treatment of chronic wounds. Such freeze-dried sponges are commercially available from Johnson & Johnson Medical Limited under the registered trade mark PROMOGRAN .

EP-A-0562862, EP-A-0562863 and EP-A-0562864 describe freeze-dried collagen sponges optionally having macroscopic substructures made of ORC embedded in the sponge. One embodiment consists of an ORC fabric laminated to a layer of collagen sponge and a layer of plasticized collagen film.

EP-A-0636378 describes medicated collagen films for use in the treatment of periodontal disease. The medicated collagen films may contain dispersed ORC fibers. The collagen matrix may contain up to 20% by weight, based on the weight of the composite of a plasticizer.

A need remains for further wound dressing materials containing ORC that can provide advantages over ORC/CMC gels or collagen/ORC sponges in terms of cost, stability, ease of manufacture and/or other properties.

The present inventors have found that a stable, conformable wound dressing material can be made by dispersing solid ORC in an aqueous gel, followed by drying the gel to produce a stable, flexible hydrogel matrix material containing dispersed ORC.

Accordingly, in a first aspect the present invention provides a wound dressing material comprising a low-moisture hydrogel matrix having oxidized cellulose distributed therein.

The term "hydrogel matrix" refers to a continuous solid phase having the oxidized cellulose dissolved or embedded therein. The Hydrogel matrix is not a freeze-dried sponge material, and preferably it has an uncompressed density of at least about 0.2g/cm^3, more preferably at least about 0.4g/cm^3.

The hydrogel matrix comprises one or more gel-forming hydrocolloids. The term "gel-forming hydrocolloid" refers to a polymeric material that absorbs water, for example from wound fluid, to form a coherent gel under physiological conditions of temperature and pH. Preferably, the hydrocolloid absorbs at least 100%w/w, more preferably at least 300%w/w of water on immersion at 25ºC for 24 hours. The matrix is preferably soluble in excess water, so as to release dispersed ORC into the wound in use. In other embodiments the matrix is water-swellable, but not water-soluble. In preferred embodiments of this type, the matrix may be formed of a hydrogel material that breaks down gradually *in vivo* so as to provide sustained release the oxidized cellulose into the wound. The term "hydrogel" in this context does not include gels or films comprising substantial amounts (e.g. more than 50% by weight) of gel-forming proteins or peptides such as collagen or gelatin. Preferably, the hydrogel material according to the present invention is substantially free of collagen and gelatin, and more preferably it is substantially free of other gel-forming proteins or peptides.

In certain embodiments the hydrogel matrix comprises a hydrocolloid material selected from the group consisting of modified celluloses, modified starches, alginates, plant gums, glycosaminoglycans, polyacrylates, polyurethanes,

polymers of vinyl alcohols, vinyl esters, vinyl ethers and carboxy vinyl monomers, meth(acrylic) acid, acrylamide, N-vinyl pyrrolidone, acylamidopropane sulfonic acid, PLURONIC (Registered Trade Mark) (block polyethylene glycol, block polypropylene glycol) polystyrene-, maleic acid, NN-dimethylacrylamide diacetone acrylamide, acryloyl morpholine, and mixtures thereof.

In preferred embodiments the hydrocolloids comprise a naturally occurring or chemically modified polysaccharide, and preferably they consists essentially of one or more naturally occurring or chemically modified polysaccharides, or mixtures thereof. Suitable chemically modified polysaccharides are selected from the group consisting carboxymethyl cellulose gels, hydroxyethyl cellulose gels, hydroxy propyl methyl cellulose gels, chitosan, low-methoxy pectins, cross-linked dextran and starch-acrylonitrile graft copolymer, starch sodium polyacrylate, and mixtures thereof. Suitable natural polysaccharides include alginic acid and its salts, pectins, galactomannans such as xanthan gum or guar gum locust bean gum, gum karaya, gum arabic, hyaluronic acid and its salts, starches, and mixtures thereof. Suitably synthetic hydrocolloids include high molecular weight polyethylene glycols and polypropylene glycols, polymers of methyl vinyl ether and maleic acid and derivatives; polyvinyl pyrrolidone, polyethylene glycols, polypropylene glycols, metal and/or ammonium salts of polyacrylic acid and/or its copolymers, metal or ammonium salts of polystyrene sulfonic acid, and mixtures thereof.

Especially preferred are compositions in which the hydrocolloids comprise, or consist essentially of, a carboxymethyl cellulose salt.

Preferably, the oxidized cellulose is an oxidized regenerated cellulose. Preferably, the oxidized cellulose is a solid material forming a distinct solid phase embedded in the matrix. However, in certain embodiments the oxidized cellulose may be in the form of dissolved soluble fragments, as described in EP-A-0907664, the entire content of which is incorporated herein by reference.

Preferably, the oxidized cellulose is in the form of fibers or fiber fragments, more preferably in the form of a woven or non-woven fabric, or discrete fibers or fiber fragments dispersed in the matrix. Preferably, the fibers or fiber fragments are randomly dispersed in the matrix.

Preferably, the wound dressing material according to the present invention further comprises a plasticizer. Suitable plasticisers include glycerol, propylene glycol, polyethylene glycol, polypropylene glycol, sorbitol, other glycols and ether glycols such as mono- or diethers of polyalkylene glycol, mono- or diester polyalkylene glycols, polyethylene glycols glycolates, ethylene glycol, diethylene glycol, triethylene glycol, propylene glycol dipelargonate and polypropylene glycol glycerol, sorbitan esters, esters of citric and tartaric acid, imidazoline derived amphoteric surfactants, lactams, amides, polyamides, quaternary ammonium compounds, esters such phthalates, adipates, stearates, palmitates, sebacates, or myristates, and combinations thereof. diisopropyl adipate, phthalates and diethyl sebacate; hydrocarbons such as liquid paraffin; ethoxylated stearyl alcohol, glycerol esters, isopropyl myristate, isotridecyl myristate, ethyl laureate, N-methylpyrrolidone, ethyl oleate, oleic acid, isopropyl adipate, isopropyl palmitate, octyl palmitate, 1,3-butanediol and mixtures thereof. Preferably, the wound dressing material comprises from about 10% to about 80% by weight of the plasticizer, more preferably from about 15% to about 60% by weight of the plasticiser.

The hydrogel matrix is a low-moisture hydrogel material. It has been found that the low moisture content stabilizes the ORC in the matrix, and provides related advantages. The wound dressing material comprises from about 1% to about 50% by weight of water, preferably from about 5% to about 40% by weight of water, more preferably from about 10% to about 30% by weight of water.

Preferably, the wound dressing material according to the present invention comprises from about 1% to about 40% by weight of the oxidized regenerated cellulose, preferably from about 5% to about 25% by weight.

Preferably, the wound dressing material according to the present invention comprises from about 1% to about 80% by weight of the one or more hydrocolloids, more preferably from about 25% to about 60% by weight.

Preferably, the wound dressing material according to the present invention further comprises one or more therapeutic agents for promoting or enhancing wound healing. The one or more therapeutic agents may be any substance suitable for the treatment of wounds, but does not include the hydrogel used to form the matrix or the oxidized cellulose itself, both of which may independently promote wound healing. In certain embodiments the therapeutic agents are selected from the group consisting of antiseptics, antibiotics, analgesics, steroids and growth factors. Preferred therapeutic agents are the antimicrobials, in particular antibiotics and antiseptics such as colloidal silver, silver sulfadiazine, povidone iodine, chlorhexidine, and mixtures thereof. Preferably, the wound dressing material according to the present invention comprises from about 0.001% to about 10% by weight of the one or more therapeutic substances, more preferably from about 0.05% to about 2% by weight.

In a second aspect, the present invention provides a wound dressing comprising a wound dressing material according to the present invention.

For example, the material according to the present invention may be made in the form of a solid sheet (or layer) for application to a wound. Preferably, the sheet is from 0.1 to 2mm thick. Preferably, the sheet has a dry basis weight of from about 10 to.about 1000g/m^2, more preferably from about 20 to about 200g/m^2, and most preferably from about 40 to about 100g/m^2. The sheet may be laminated to a solid polymer film, for example a perforated wound contacting film of ethylene methyl acrylate (EMA).

The sheet or layer of the material according to the present invention may be continuous or apertured. Typically, the apertures make up from about 0.1% to about 50% of the area of the sheet (preferably of the wound facing area of the sheet) before swelling, more typically from about 1% to about 30% of the area of

the sheet before swelling, preferably from about 10% to about 25%, and more preferably from about 10% to about 20%. of the area of the sheet before swelling.

It is an advantage of the present invention that the low moisture hydrogels have a conformable and slightly resilient feel that makes such sheets suitable for handling and application to a wound surface.

Preferably, the wound dressing comprises an absorbent layer and/or a backing layer in addition to the sheet of material according to the present invention, in which case the sheet is preferably the wound-facing top sheet of the dressing.

Preferably, the dressing further comprises a backing layer over the back face of the dressing sheet. The backing layer preferably provides a barrier to passage of microorganisms through the dressing and further preferably blocks the escape of wound fluid from the dressing. The backing layer may extend beyond at least one edge of the absorbent layer to provide an adhesive-coated margin adjacent to the said edge for adhering the dressing to a surface, such as to the skin of a patient adjacent to the wound being treated. An adhesive-coated margin may extend around all sides of the absorbent layer, so that the dressing is a so-called island dressing. However, it is not necessary for there to be any adhesive-coated margin.

Preferably, the backing layer is substantially liquid-impermeable. The backing sheet is preferably semipermeable. That is to say, the backing sheet is preferably permeable to water vapour, but not permeable to liquid water or wound exudate. Preferably, the backing sheet is also microorganism-impermeable. Suitable continuous conformable backing sheets will preferably have a moisture vapor transmission rate (MVTR) of the backing sheet alone of 300 to 5000 g/m^2/24hrs, preferably 500 to 2000 g/m^2/24hrs at 37.5 °C at 100% to 10% relative humidity difference. The backing sheet thickness is preferably in the range of 10 to 1000 micrometers, more preferably 100 to 500 micrometers.

Suitable polymers for forming the backing sheet include polyurethanes and poly alkoxyalkyl acrylates and methacrylates such as those disclosed in GB-A-1280631. Preferably, the backing sheet comprises a continuous layer of a high density blocked polyurethane foam that is predominantly closed-cell. A suitable backing sheet material is the polyurethane film available under the Registered Trade Mark ESTANE 5714F.

The adhesive (where present) layer should be moisture vapor transmitting and/or patterned to allow passage of water vapor therethrough. The adhesive layer is preferably a continuous moisture vapor transmitting, pressure-sensitive adhesive layer of the type conventionally used for island-type wound dressings, for example, a pressure sensitive adhesive based on acrylate ester copolymers, polyvinyl ethyl ether and polyurethane as described for example in GB-A-1280631. The basis weight of the adhesive layer is preferably 20 to 250 g/m^2, and more preferably 50 to 150 g/m^2. Polyurethane-based pressure sensitive adhesives are preferred.

Preferably, the adhesive layer extends outwardly from the absorbent layer and the envelope to form an adhesive-coated margin on the backing sheet around the adhesive layer as in a conventional island dressing.

The area of the optional absorbent layer is typically in the range of from 1cm^2 to 200cm^2, more preferably from 4cm^2 to 100cm^2.

The optional absorbent layer may be any of the layers conventionally used for absorbing wound fluids, serum or blood in the wound healing art, including gauzes, nonwoven fabrics, superabsorbents, hydrogels and mixtures thereof. Preferably, the absorbent layer comprises a layer of absorbent foam, such as an open celled hydrophilic polyurethane foam prepared in accordance with EP-A-0541391, the entire content of which is expressly incorporated herein by reference. In other embodiments, the absorbent layer may be a nonwoven fibrous web, for example a carded web of viscose staple fibers. The basis weight of the absorbent layer may be in the range of 50-500g/m^2, such as 100-400g/m^2. The uncompressed thickness of the absorbent layer may be in the range of from

0.5mm to 10mm, such as 1mm to 4mm. The free (uncompressed) liquid absorbency measured for physiological saline may be in the range of 5 to 30 g/g at 25°

Preferably, the wound dressing according to the invention is sterile and packaged in a microorganism-impermeable container.

In a third aspect, the present invention provides the use of a wound dressing material according to the present invention, for the preparation of a dressing for use in the treatment of wounds.

In a further aspect, the present invention provides a method of treatment of a wound in a mammal, comprising applying to the wound an effective amount of a wound dressing material according to the present invention.

Preferably, the wound is a chronic wound such as a venous ulcer, a diabetic ulcer or a decubitis ulcer.

In a further aspect, the present invention provides a method of making a wound dressing, comprising the steps of: providing an aqueous gel; immersing or dispersing an oxidized cellulose in the aqueous gel; followed by drying the gel to a moisture content of less than about 60% by weight.

Preferably, the method according to this aspect of the invention is adapted to the manufacture of a wound dressing material according to the present invention.

The aqueous gel preferably comprises at least about 90%w/w of water, more preferably at least about 95%w/w of water. The step of drying is preferably carried out under mild conditions. Preferably, the step of drying is applied without applying a vacuum, and preferably the step of drying is carried out at a temperature of from about 0 to about 100ºC, more preferably from about 20º to about 80ºC, and most preferably at from about 35º to about 65ºC. The material

may be shaped, for example by molding or extrusion, either before, after, or in the course of the drying step.

It will be appreciated that any features that are described as alternatives or preferred features in connection with any one of the above aspects of the invention are also likewise alternatives or preferred in relation to any other aspect of the invention.

Specific embodiments of the invention will now be described further, by way of example.

Example 1

Milled ORC fibers prepared as described in EP-A-1153622 (the entire content of which is incorporated herein by reference) were dispersed at a concentration of 2.17% w/w in KY Jelly (registered trade mark). KY Jelly is a commercial hydrogel manufactured by Johnson & Johnson. The exact formulation is as follows, in percentages by weight:

Propylene glycol	3.750
Glycerine	11.250
Monosodium Dihydrogen orthophosphate (buffer)	0.875
Disodium hydrogen orthophosphate (buffer)	0.045
Methyl butex (preservative)	0.100
Propyl ester (preservative)	0.040
Hydroxyethyl cellulose	2.133
EDTA	0.021
Water	81.792

The resulting gel was spread in a petri dish to a depth of 5mm and dried in air immediately at 37°C for 48 hours. The resulting dried hydrogel layer was flexible, conformable, and slightly elastic. The ORC in the hydrogel matrix appeared to be completely stable for at least six weeks at 37°C in ambient atmosphere. That is to say, the ORC fibers when viewed under a microscope did not exhibit any swelling or dissolution.

Example 2

The procedure of Example 1 was repeated, but with replacement of the KY jelly with INTRASITE (Registered Trade Mark) gel produced by Smith & Nephew Healthcare Ltd. This is an aqueous gel which contains 2.3% of a modified CMC and 20% of propylene glycol.

The above embodiments have been described by of example only. Many other embodiments falling within the scope of the accompanying claims will be apparent to the skilled reader.

CLAIMS

1. A wound dressing material comprising a low-moisture hydrogel matrix having oxidized cellulose distributed therein.

2. A wound dressing according to claim 1, wherein the oxidized cellulose is an oxidized regenerated cellulose.

3. A wound dressing according to claim 2, wherein the oxidized regenerated cellulose is in the form of a woven or non-woven fabric, or discrete fibers.

4. A wound dressing according to any preceding claim, wherein the hydrogel matrix comprises a hydrogel selected from the group consisting of modified celluloses, modified starches, alginates, plant gums, gelatins, glycosaminoglycans, polyacrylates, polyurethanes, and mixtures thereof.

5. A wound dressing according to claim 4, wherein the hydrogel is selected from the group consisting carboxymethyl cellulose salts, alginate salts, gelatins, hyaluronic acid and its salts, xanthan gum, guar gum, and mixtures thereof.

6. A wound dressing according to any preceding claim, wherein the wound dressing material further comprises a plasticizer.

7. A wound dressing according to claim 6, wherein the plasticizer is selected from the group consisting of glycerol, propylene glycol, polyethylene glycol, polypropylene glycol, sorbitol, other glycols and ether glycols such as mono- or diethers of polyalkylene glycol, mono- or diester polyalkylene glycols, polyethylene glycols glycolates, ethylene glycol, diethylene glycol, triethylene glycol, propylene glycol dipelargonate and polypropylene glycol glycerol, sorbitan esters, esters of citric and tartaric acid, imidazoline derived amphoteric surfactants, lactams, amides, polyamides, quaternary ammonium compounds, esters such phthalates, adipates, stearates, palmitates, sebacates, or myristates, and combinations thereof. diisopropyl adipate, phthalates and diethyl sebacate; hydrocarbons such

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as liquid paraffin; ethoxylated stearyl alcohol, glycerol esters, isopropyl myristate, isotridecyl myristate, ethyl laurate, N-methylpyrrolidone, ethyl oleate, oleic acid, isopropyl adipate, isopropyl palmitate, octyl palmitate, 1,3-butanediol and mixtures thereof.

8. A wound dressing according to claim 6 or 7, wherein the wound dressing material comprises from about 10% to about 80% by weight of the plasticizer.

9. A wound dressing material according to any preceding claim, wherein the wound dressing material comprises from about 1% to about 50% by weight of water.

10. A wound dressing material according to any preceding claim, wherein the material comprises from about 1% to about 40% by weight of the oxidized regenerated cellulose.

11. A wound dressing material according to any preceding claim, wherein the material comprises from about 1% to about 60% by weight of the one or more hydrocolloids.

12. A wound dressing material according to any preceding claim, further comprising one or more therapeutic agents.

13. A wound dressing comprising a wound dressing material according to any of claims 1 to 12.

14. A wound dressing according to claim 13, which is in the form of a sheet.

15. A wound dressing according to claim 13 or 14, which is sterile and packaged in a microorganism-impermeable container.

16. Use of a wound dressing material according to any of claims 1 to 12, for the preparation of a dressing for use in the treatment of wounds.

17. Use according to claim 15, wherein the wound is a chronic wound.

18. A method of making a wound dressing, comprising the steps of:

providing an aqueous gel;

immersing or dispersing an oxidized cellulose in the aqueous gel; followed by

drying the gel to a moisture content of less than about 50% by weight.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L26/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, COMPENDEX, BIOSIS, EMBASE, INSPEC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/24841 A (CULLEN BREDA MARY ; JOHNSON & JOHNSON MEDICAL LTD (GB); SILCOCK DEREK) 12 April 2001 (2001-04-12) example 3 claims	1-18
X	EP 0 815 879 A (JOHNSON & JOHNSON MEDICAL) 7 January 1998 (1998-01-07) examples 6,7 claims 1-18	1-18
X	WO 98/00180 A (WATT PAUL WILLIAM ; HARVEY WILSON (GB); LORIMER ELAINE (GB); JOHNSON &) 8 January 1998 (1998-01-08) cited in the application example 6	1,2,4,5, 9-11,13, 15,16

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Muñoz, M

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INTERNATIONAL SEARCH REPORT

national Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 696 101 A (HOPKINS WARREN KENT ET AL) 9 December 1997 (1997-12-09) example 2	1,2, 9-11,16, 18
E	WO 2004/026200 A (CULLEN BREDA MARY ; JOHNSON & JOHNSON MEDICAL LTD (GB); SILCOCK DEREK) 1 April 2004 (2004-04-01) example 3	1,2,4,5, 9-11,13, 15,16

INTERNATIONAL SEARCH REPORT

national Application No
..T/GB2004/000892

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 0124841	A	12-04-2001	GB	2354708 A	04-04-2001
			AU	7538100 A	10-05-2001
			EP	1216066 A1	26-06-2002
			WO	0124841 A1	12-04-2001
			JP	2003511099 T	25-03-2003
EP 0815879	A	07-01-1998	AU	725479 B2	12-10-2000
			AU	2754097 A	22-01-1998
			BR	9703773 A	10-11-1998
			CA	2208939 A1	28-12-1997
			CN	1181980 A	20-05-1998
			EP	0815879 A2	07-01-1998
			JP	10066723 A	10-03-1998
WO 9800180	A	08-01-1998	GB	2314842 A	14-01-1998
			AT	247493 T	15-09-2003
			AU	737809 B2	30-08-2001
			AU	3269297 A	21-01-1998
			BR	9710177 A	18-01-2000
			CA	2258990 A1	08-01-1998
			CZ	9804251 A3	12-05-1999
			DE	69724257 D1	25-09-2003
			EP	1325754 A1	09-07-2003
			EP	0918548 A1	02-06-1999
			ES	2205237 T3	01-05-2004
			WO	9800180 A1	08-01-1998
			JP	2000513258 T	10-10-2000
			KR	2000022287 A	25-04-2000
			PL	330824 A1	07-06-1999
			PT	918548 T	28-11-2003
US 5696101	A	09-12-1997	WO	9738737 A1	23-10-1997
WO 2004026200	A	01-04-2004	GB	2393120 A	24-03-2004
			WO	2004026200 A2	01-04-2004